

Enantioselective Synthesis of Oasomycin A, Part I: Synthesis of the C1–C12 and C13–C28 Subunits**

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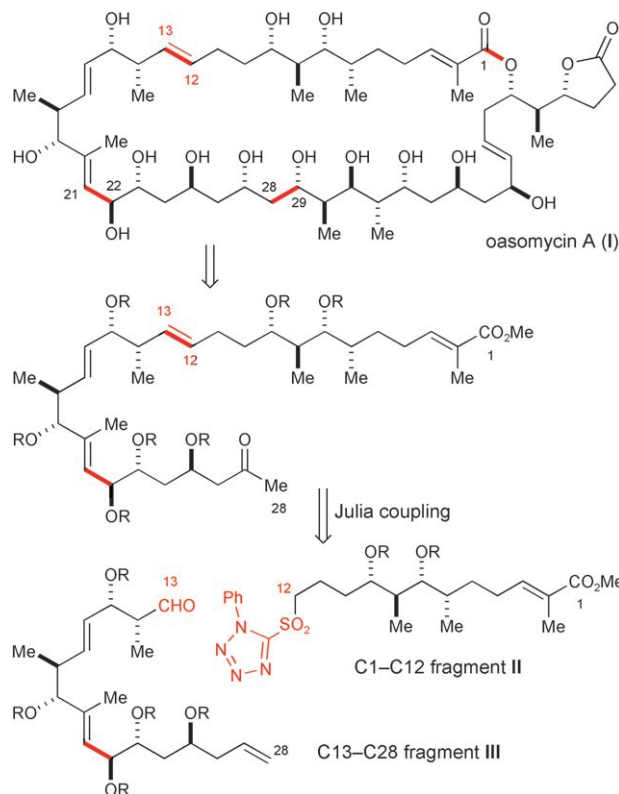
Dedicated to Professor Y. Kishi on the occasion of his 70th birthday.

Oasomycin A (**I**) is a member of the desertomycin family of macrolide natural products and was isolated in 1993 by Thiericke and co-workers during the screening of secondary metabolites of *Streptovercillium baldacii*.^[1] The overall structure of oasomycin A was established through extensive NMR spectroscopic studies and by direct comparison to other members of the desertomycin family.^[1a] In 2001, Kishi and co-workers issued a proposal for the relative and absolute stereochemistry of oasomycin A through the use of their “universal NMR database” (Scheme 1).^[2] To validate the structural assignment of oasomycin A, we decided to pursue the synthesis of the reported structure, **I**.

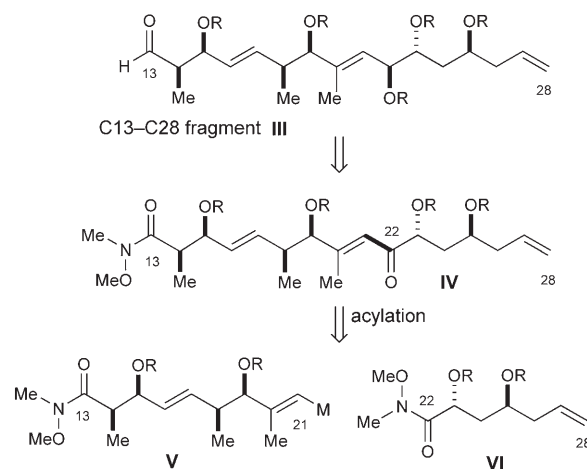
Herein, and in the following Communications,^[23] we describe our efforts which culminated in the synthesis of oasomycin A (**I**) and confirm the stereochemical assignment by Kishi and co-workers. First, we describe the synthesis of the C1–C12 and C13–C28 subunits **II** and **III**, respectively, which will be united by using the Julia coupling reaction (Scheme 1).

Our plan for the synthesis of the C13–C28 fragment **III** is outlined in Scheme 2. Aldehyde **III** could be derived from a chelate-controlled reduction of the α,β -unsaturated ketone **IV**, which in turn can be disconnected at the C21–C22 bond to afford fragments **V** and **VI**. We predict successful union of these two fragments because of the greater reactivity of the Weinreb amide **VI**, which is required to avoid self-condensation of **V** ($M = \text{Li}, \text{MgX}$). This prediction is based on the supposition that the inductive effect of the α -alkoxy substituent should elevate the amide reactivity of **VI** above that of its reaction partner **V**.

Synthesis of subunit **II** commenced with the aldol addition of known β -ketoimide **1**^[3] to aldehyde **2**,^[4] which afforded the desired *anti,anti* aldol adduct^[5] as an 84:16 mixture of



Scheme 1. Retrosynthetic analysis of oasomycin A (**I**).

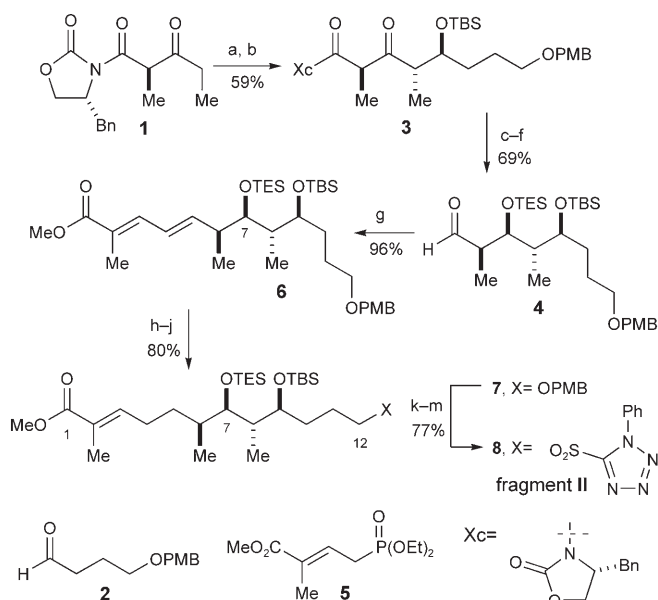


Scheme 2. Retrosynthesis of the C13–C28 subunit **III**.

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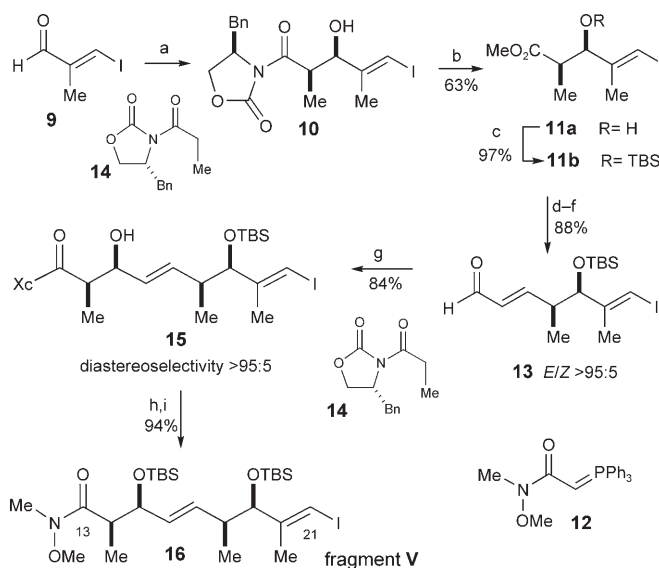
Scheme 3. Synthesis of the C1–C12 fragment II. Reagents and conditions: a) Cy_2BCl , Me_2NEt , Et_2O , -78°C ; then **2**, Et_2O , -78°C , (84:16 d.r.); b) TBSOTf, lutidine, CH_2Cl_2 , -78°C , (59%, 2 steps); c) $\text{Zn}(\text{BH}_4)_2$, CH_2Cl_2 , $-78 \rightarrow -25^\circ\text{C}$, (10:1 d.r.); d) TESOTf, lutidine, CH_2Cl_2 , -78°C ; e) EtSLi, THF, -20°C ; f) DIBALH, CH_2Cl_2 , -90°C , (69%, 4 steps); g) **5**, $n\text{BuLi}$, THF, -78°C ; then **4**, 96%; h) CSA, $\text{MeOH}/\text{CH}_2\text{Cl}_2$ 1:1; i) Crabtree cat. (10 mol%), CH_2Cl_2 , RT; j) TESOTf, lutidine, CH_2Cl_2 , -78°C , (80%, 3 steps); k) DDQ, $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ 12:1; l) 1-phenyl-1H-tetrazole-5-thiol, DEAD, PPh_3 , THF; m) $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}$, H_2O_2 , EtOH, (77%, 3 steps). Bn = benzyl, cod = cycloocta-1,5-diene, CSA = camphorsulfonic acid, Cy = cyclohexyl, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DEAD = diethyl azodicarboxylate, DIBALH = diisobutylaluminum hydride, PMB = 4-methoxybenzyl, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, Tf = trifluoromethanesulfonyl.

diastereomers (Scheme 3). This mixture was immediately silylated (TBSOTf, lutidine) to provide **3** as a single diastereomer after flash chromatography. Successive chelate-controlled reduction of **3** with $\text{Zn}(\text{BH}_4)_2$ (10:1 d.r.),^[6,7] alcohol protection (TESOTf, lutidine), removal of the oxazolidinone auxiliary (EtSH, $n\text{BuLi}$ THF, -20°C), and reduction of the derived thioester with DIBALH afforded aldehyde **4** (69%, 4 steps). Aldehyde **4** was condensed with the known phosphonate **5**^[8] under standard Horner–Wadsworth–Emmons conditions to afford diene **6** (96%, *E/Z* 10:1).

The selective hydrogenation of the *trans* Δ^4 olefin in **6** was complicated by the generation of inseparable side products that resulted from overreduction.^[9] This problem was overcome by resorting to a hydroxy-directed hydrogenation. Selective deprotection of the C7 hydroxy group in **6** (CSA, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 1:1) and hydrogenation of the derived homoallylic alcohol with the Crabtree catalyst $[\text{Ir}(\text{cod})\text{py}(\text{PCy}_3)]\text{PF}_6$ ^[10] afforded a now-separable 11:1 mixture of the desired olefin and the fully hydrogenated by-product.^[11] The C7 hydroxy group was then reprotected using TESOTf, thus affording **7** (80%, 3 steps). Methyl ester **7** was next transformed into sulfone **8** (synthon II, Scheme 1) by removal of the C12 PMB group (DDQ, $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ 12:1), Mitsunobu reaction of the resulting primary alcohol with 1-phenyl-1H-

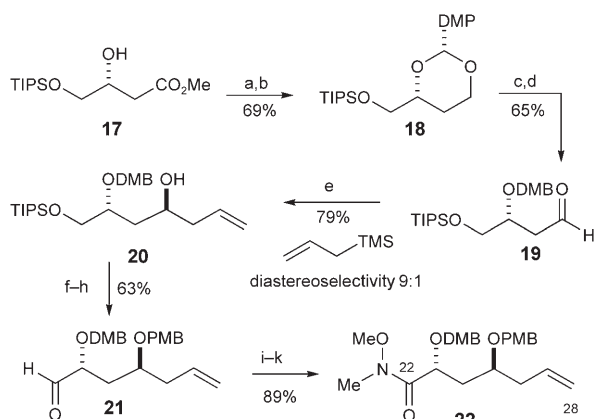
tetrazole-5-thiol, and oxidation (H_2O_2 , $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}$, EtOH)^[12,13] of the resulting sulfide.

Synthesis of the C13–C21 fragment **V** (Scheme 2) began with the aldol addition of the (*Z*)-dibutylboron enolate of imide **14** to known aldehyde **9**^[14] to afford the expected aldol adduct **10** (Scheme 4). The chiral auxiliary was removed with sodium methoxide in methanol (63%, 2 steps) to afford the known ester **11a**.^[14] This ester **11a** was successively silylated to the known TBS ether **11b**^[14] (TBSOTf, lutidine) and then transformed into the unstable α,β -unsaturated aldehyde **13** by a reduction/Wittig olefination/reduction sequence in 88% yield over the three steps. Reaction of the (*Z*)-dibutylboron enolate of chiral imide **14** with aldehyde **13** proceeded smoothly to give aldol adduct **15** (84%, >95:5 d.r.). The chiral auxiliary was then removed ((MeO)MeNH·HCl, AlMe_3), and the resulting alcohol protected as the TBS ether (TBSOTf, lutidine, 94%, 2 steps) to complete the synthesis of the C13–C21 fragment **16**.



Scheme 4. Synthesis of the C13–C21 fragment **V**. Reagents and conditions: a) **14**, Bu_2BOTf , NEt_3 , CH_2Cl_2 , $-78 \rightarrow 0^\circ\text{C}$; then **9**, CH_2Cl_2 , -78°C ; b) NaOMe, $\text{MeOH}/\text{CH}_2\text{Cl}_2$, -25°C , (63%, 2 steps); c) TBSOTf, lutidine, CH_2Cl_2 , -10°C , 97%; d) DIBALH, toluene, $-90 \rightarrow -80^\circ\text{C}$; e) **12**, CH_2Cl_2 ; f) DIBALH, CH_2Cl_2 , -90°C , (88%, 3 steps); g) **14**, Bu_2BOTf , NEt_3 , CH_2Cl_2 , $-10 \rightarrow 0^\circ\text{C}$; then **13**, CH_2Cl_2 , -78°C , 84%; h) AlMe_3 , $\text{Me}(\text{MeO})\text{NH}\cdot\text{HCl}$, THF, 0°C ; i) TBSOTf, lutidine, CH_2Cl_2 , -10°C , (94%, 2 steps).

The synthesis of the C22–C28 fragment (Scheme 5) began with LiAlH_4 reduction of the *D*-malic acid derivative **17**,^[15] followed by diol protection to form the 3,4-dimethoxybenzylidene acetal **18** (69%, 2 steps). The regioselective reduction of **18** was accomplished with DIBALH, and the primary alcohol was then oxidized under Parikh–Doering conditions^[16] to provide aldehyde **19** (65%, 2 steps). Allylation of **19** under chelate-controlled conditions (AlMe_2Cl , allyltrimethylsilane) afforded **20** as a 9:1 mixture of diastereomeric alcohols that were separable by medium pressure liquid chromatography.^[17] Protection of **20** as its PMB ether (PMBBr, NaHMDS), removal of the TIPS group with

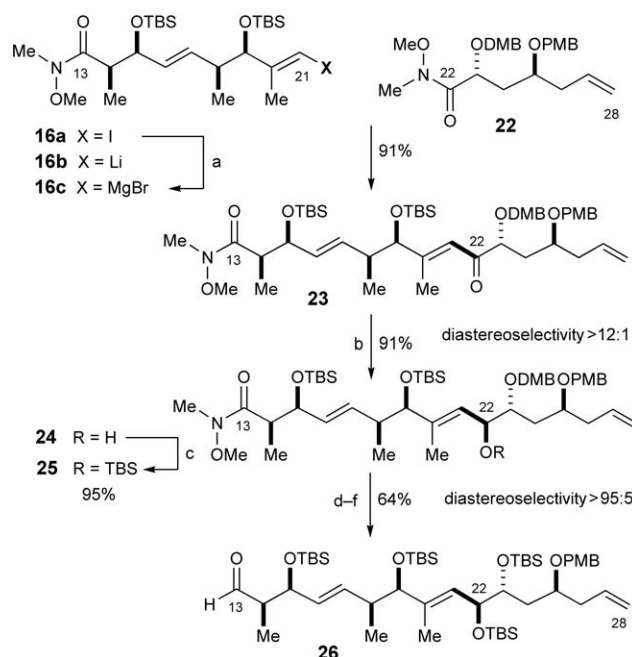


Scheme 5. Synthesis of the C22–C28 fragment **22**. Reagents and conditions: a) LiAlH_4 , Et_2O , 0°C ; b) $\text{DMPCH}(\text{OMe})_2$, CSA, CH_2Cl_2 , (69%, 2 steps); c) DIBALH , CH_2Cl_2 , $-78 \rightarrow -10^\circ\text{C}$; d) $\text{SO}_3 \cdot \text{Py}$, NEt_3 , $\text{DMSO}/\text{CH}_2\text{Cl}_2$ 1:1, -10°C , (65%, 2 steps); e) AlMe_2Cl (2 equiv), $\text{CH}_2=\text{CHCH}_2\text{TMS}$, CH_2Cl_2 , -93°C , (9:1 d.r., 79% yield); f) PMBBr , NaHMDS , TBAI , DMF/THF 1:2, -15°C ; g) TBAF , THF , 0°C ; h) $\text{SO}_3 \cdot \text{Py}$, NEt_3 , $\text{DMSO}/\text{CH}_2\text{Cl}_2$ 1:1, -10°C , (63%, 3 steps); i) NaClO_2 , NaH_2PO_4 , 2-methylbut-2-ene, $t\text{BuOH}/\text{H}_2\text{O}$ 3:2; j) TMSCHN_2 , MeOH/PhH 10:1; k) $\text{Me}(\text{MeO})\text{NH} \cdot \text{HCl}$, $i\text{PrMgCl}$, THF , -10°C , (89%, 3 steps). DMB = 3,4-dimethoxybenzyl, DMP = 3,4-dimethoxyphenyl, HMDS = 1,1,1,3,3,3-hexamethyldisilazane, Py = pyridine, TBA = *tert*-butylammonium, TIPSO = triisopropylsilyl, TMS = trimethylsilyl.

TBAF, followed by Parikh–Doering oxidation afforded aldehyde **21** (63%, 3 steps). Aldehyde **21** could then be converted into the Weinreb amide **22** by a three-step sequence involving Kraus–Pinnick oxidation,^[18] methylation (TMSCHN_2 , MeOH/PhH), and amidation by using the Merck procedure (89%, 3 steps).^[19]

The coupling of the C13–C21 and C22–C28 fragments gave us the opportunity to test the relative reactivities of Weinreb amides **16** and **22** (Scheme 6). Metalation of vinyl iodide **16a** afforded vinyl lithium **16b**. We predicted that this intermediate would react with **22** rather than with itself based on the observation that α -alkoxycarbonyl compounds are usually more reactive electrophiles than the corresponding α -alkylcarbonyl derivatives.^[20] The desired chemoselectivity was indeed achieved; however, transmetalation of **16b** to the corresponding alkenylmagnesium **16c** was required to attenuate the reactivity of the nucleophile. Thus, under the aforementioned conditions, the coupling of **16** and **22** afforded the coupled C13–C28 product **23**^[21] in 91% yield. Ketone **23** was then reduced under chelate-controlled conditions ($\text{Zn}(\text{BH}_4)_2$) to give alcohol **24** in 91% yield (12:1 d.r.).^[7] Protection of **24** as its derived TBS ether (TBSOTf, lutidine) afforded **25** (95% yield), which was then elaborated to aldehyde **26** by a three-step sequence: selective deprotection (DDQ, $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$) of the 3,4-dimethoxybenzyl ether at C23,^[22] protection of the resulting alcohol with TBSOTf, and reduction of the Weinreb amide with DIBALH (64%, 3 steps).

Thus we have described the stereoselective synthesis of the C1–C12 and C13–C28 fragments of oasomycin A, a sequence that allowed us to prepare significant quantities of these materials. The following Communications^[23] describe



Scheme 6. Synthesis of the C13–C28 fragment **26**. Reagents and conditions: a) 1. **16** (1.00 equiv), $n\text{BuLi}$ (1.09 equiv), Et_2O , -78°C ; 2. $\text{MgBr}_2 \cdot \text{Et}_2\text{O}$ (1.31 equiv), $\text{Et}_2\text{O}/\text{THF}$ $-78 \rightarrow -20^\circ\text{C}$; 3. **22** (0.965 equiv), $\text{Et}_2\text{O}/\text{THF}$, $-20 \rightarrow 0^\circ\text{C}$, 91%; b) $\text{Zn}(\text{BH}_4)_2$, $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$, -30°C , 91%; c) TBSOTf, lutidine, THF , 0°C , 95%; d) DDQ, $\text{H}_2\text{O}/\text{CH}_2\text{Cl}_2$ 1:10, -3°C ; e) TBSOTf, lutidine, CH_2Cl_2 , 0°C ; f) DIBALH, toluene, -78°C , (64%, 3 steps).

the synthesis of the C29–C46 fragment and the assembly of the fragments to afford oasomycin A.

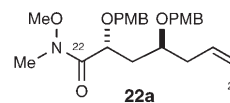
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